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Regulation of nuclear actin dynamics in development and disease

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Abstract

Actin has essential functions both in the cytoplasm and in the nucleus, where it has been linked to key nuclear processes, from transcription to DNA damage response. The multifunctional nature of actin suggests that the cell must contain mechanisms to accurately control the cellular actin balance. Indeed, recent results have demonstrated that nuclear actin levels fluctuate to regulate the transcriptional activity of the cell and that controlled nuclear actin polymerization is required for transcription activation, cell cycle progression, and DNA repair. Intriguingly, aberrant nuclear actin regulation has been observed, for example, in cancer, signifying the importance of this process for cellular homeostasis. This review discussed the latest research on how nuclear actin is regulated, and how this influences actin-dependent nuclear processes.

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Actin, nuclear actin, transcription, DNA damage response, SRF.

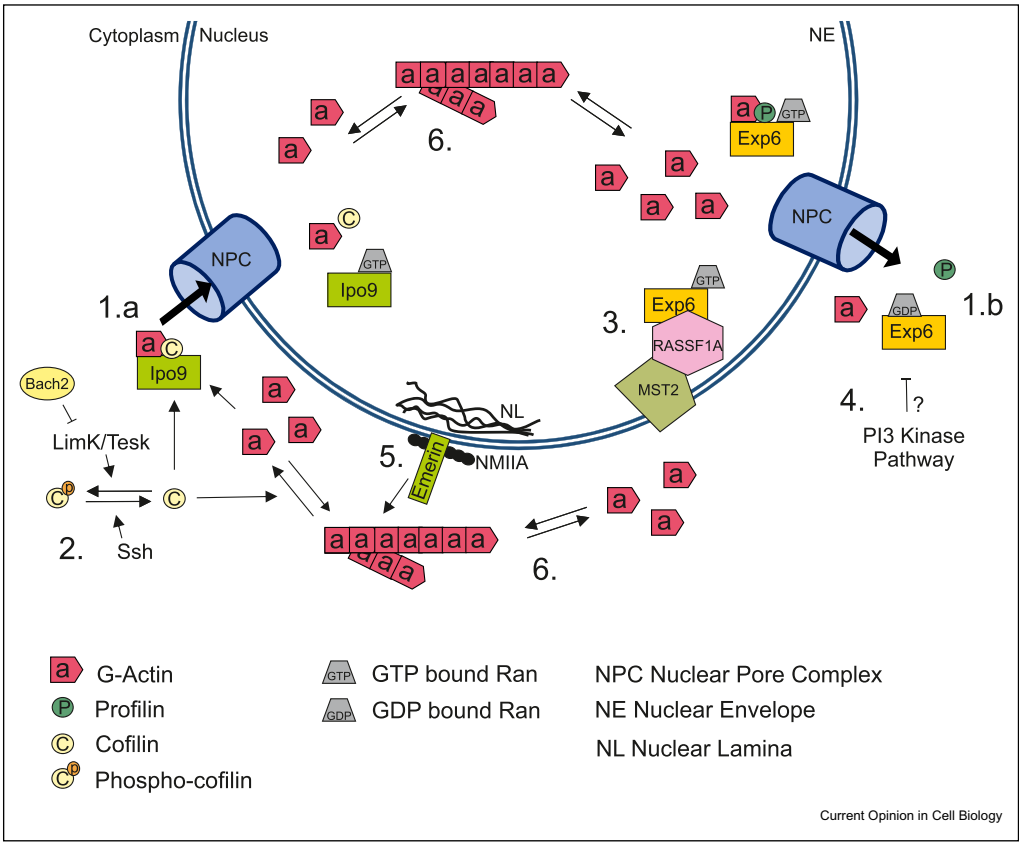
Introduction

In the cytoplasm, actin is an essential part of the cytoskeleton, and contributes to biological processes such as cell division, cell motility, and sensing of environmental forces. The ability to polymerize from monomers (G-actin) into thin filaments (F-actin) is critical for these functions, providing the forces for movement. Consequently, actin dynamics are very tightly regulated in the cells by numerous actin-binding proteins (ABPs) and signaling pathways [1]. Actin was found to be present in the nucleus over 40 years ago. However, for a long time the concept of nuclear actin was treated with a great skepticism, mainly owing to the lack of the experimental tools for studying nuclear actin. During the past two decades, the discovery of a dedicated nucleocytoplasmic shuttling system for actin [2,3] and the functional requirement for actin during crucial nuclear processes have invigorated this research field. Actin has been linked to many processes that regulate gene expression. Actin interacts with all transcribed genes [4], copurifies with all three eukaryotic RNA polymerases [5–7], is a *bona fide* component of many chromatin-remodeling complexes (reviewed by Klages-Mundt et al. [8]) and also regulates the activity of specific transcription factors. For example, the activity of a serum response factor (SRF) is controlled by actin dynamics via SRF coactivator, myocardin-related transcription factor A (MRTF-A, also known as MAL or MKL1) [9] and requires nuclear actin assembly mediated by mDia1/2 formins [10,11]. Actin has been suggested to operate during several steps of the transcription process, and this is also supported by a recent mass spectrometry–based analysis, which identified proteins involved in transcription preinitiation, elongation, and pre-mRNA processing, as putative nuclear actin interactors [12]. However, the exact molecular mechanisms await further studies. In chromatin remodeling complexes, actin operates as a monomer [8], but the polymerization status of nuclear actin during other transcription-related processes remains enigmatic. In addition to gene expression, actin is linked to DNA replication [13] and several recent studies support the role of nuclear actin in DNA damage response [14–17], as well as long-range chromatin motion [18]. During these genome maintenance tasks, the ability of nuclear actin to polymerize seems to be crucial. The multifunctional nature of actin in the nucleus, together with its essential tasks in the cytoplasm, indicate that cells must contain sophisticated mechanisms to regulate the balance between cytoplasmic and nuclear actin pools, as well as also between monomeric and filamentous actin pools in either compartment. In this review, we will discuss the recent results on how nuclear actin is regulated and its implications to the actin-dependent nuclear processes.

Regulation of nuclear actin levels for gene expression and nuclear support

Our earlier studies have shown that actin constantly and rapidly shuttles in and out of the nucleus by an active transport mechanism (Figure 1.). Actin monomers are imported into the nucleus by importin-9 in a complex with cofilin [3] and exported by exportin-6 in a complex with profilin [2]. The controlled balance between cytoplasmic and nuclear actin is crucial for the cell, and its disruption inhibits transcription [3]. Similarly, mouse embryonic fibroblast derived from β-actin−/− mice, and thus lacking the main nonmuscle isoform of actin, display major defects in chromatin organization and gene expression [19] and also fail to induce neuronal gene expression programs upon reprogramming to neurons [20], supporting the requirement for balanced expression levels of different actin isoforms for proper gene expression. The availability of actin monomers limits the nuclear transport rate of actin in both directions [3]. Thus, signaling pathways affecting actin polymerization status in either compartment can influence nuclear actin levels. For instance, mechanical strain causes enrichment of emerin at the outer nuclear membrane, where it regulates, together with nonmuscle myosin IIA, the formation of a perinuclear F-actin ring. This leads to reduction in import-compatible actin monomers, and consequently decreased nuclear actin levels, which attenuates transcription and is required for polycomb-dependent gene silencing [21]. Interestingly, the subcellular localization of emerin may regulate

Figure 1



Maintaining the actin balance in the nucleus. (1) Actin is actively imported into the nucleus by importin-9 (Ipo9) together with cofilin (a.) and exported out by exportin-6 (Exp6) together with profilin (b.). Importin-9 and exportin-6 binding to their cargo is regulated by Ran-GTP, which exists at high levels in the nucleus to promote export complex formation and to disassemble the nuclear import complexes. (2) Phosphorylation state of cofilin plays an important role in nuclear import of actin. Tes and Lim kinases phosphorylate and inactivate cofilin, whereas Slingshot (Ssh) activates it by dephosphorylation. Bach2 inhibits TesK levels to maintain active cofilin. (3) RASSF1A promotes the exportin-6–mediated nuclear export of actin and profilin. RASSF1A localizes to the nuclear envelope in association with the MST2 kinase and forms a complex with exportin-6 and Ran-GTPase. (4) Phosphoinositide 3-kinase (PI3K) pathway regulates exportin-6 levels and thus alters nuclear actin levels. However, the exact molecular mechanisms are not yet understood, and thus the question mark. (5) Emerin can regulate nuclear actin levels upon mechanical stress. Emerin and nonmuscle myosin IIA (NMIIA) promote local actin polymerization at the outer nuclear membrane that leads to decreased levels of free import-compatible G-actin. (6) The availability of actin monomers affects the nuclear actin levels in and outside the nucleus. In addition to polymerization, the availability of actin monomers also depends on other binding events of actin. RASSF1, Ras association domain family 1 isoform A.

nuclear actin also in other contexts. Emerin is a transmembrane protein that most often localizes to the inner nuclear membrane to regulate gene expression, cell signaling, and chromatin organization [22]. In addition to perinuclear actin polymerization [21], also loss of lamin A/C expression leads to mislocalization of emerin to the endoplasmic reticulum and outer nuclear membrane, leading to defects in nuclear actin functions and decreased expression of MRTF-A-SRF target genes [23].

First studies that describe regulated nuclear export of actin were performed in the *Xenopus laevis* oocyte. In these cells, exportin-6 levels are downregulated by a post-transcriptional mechanism, leading to high nuclear actin levels. This leads to the assembly of a nuclear actin meshwork, which helps to maintain the integrity of the huge oocyte nuclei [24] and also protects the ribonucleoprotein droplets against gravity [25]. Regulation of exportin-6 activity, by the phosphatidylinositol 3-kinase signaling pathway, has been reported in human mammary epithelial cells in response to the basement membrane component laminin-111 [26,27]. This decreases nuclear actin levels, consequently leading to decreased transcription and quiescence [27]. Interestingly, this pathway seems to be deregulated in cancer, leading to loss of tissue homeostasis [26]. Exportin-6 activity can also be regulated by its binding partners. Ras association domain family 1 isoform A (RASSF1) is required for the association of exportin-6 with the Ran-GTPase, which is necessary to form the export complex. Functionally, the pathway is required for the appropriate control of the MRTF-A-SRF transcription complex and downstream cytoskeletal gene expression. Intriguingly, also this pathway is deregulated in many cancers because Ras association domain family 1 isoform A is frequently lost in cancer cells owing to promoter hypermethylation [28].

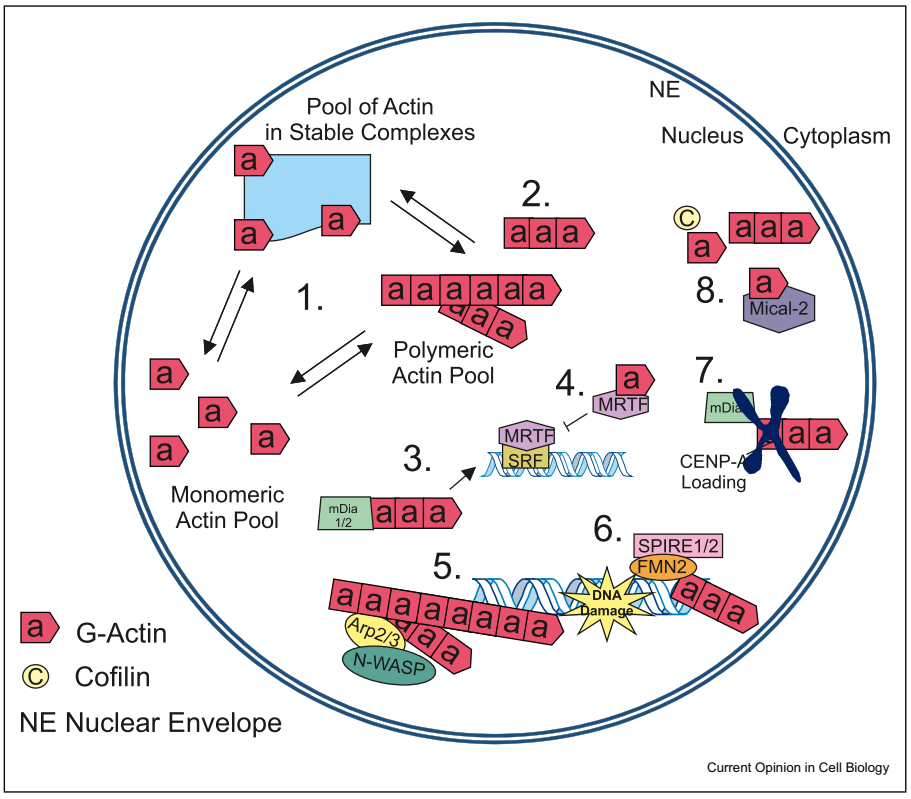
Nuclear actin levels have been shown to fluctuate also, for example, during differentiation of HL-60 cells to macrophages [29] and upon several conditions that cause cellular stress including heat shock, ATP-depletion, and DMSO treatment (reviewed by Viita et al. [30]). However, the mechanisms and signaling pathways impinging on nuclear actin control in these conditions have not been elucidated. Nevertheless, cofilin may play a crucial role here. In fly embryo, a heat-induced actin-stress response induces the assembly of intranuclear actin rods in a process that is dependent on free actin monomer levels and cofilin [31]. Because the heat stress also induces alterations in the cytoplasmic actin networks, this study highlights the need to balance cytoplasmic and nuclear actin functions for proper embryogenesis especially in response to environmental stress. The functional implications of the intranuclear actin rods during stress remain to be investigated. The importance of cofilin in nuclear actin control was also highlighted by a genome wide RNAi screen in cultured *Drosophila* cells that identified several novel regulators of cofilin phosphorylation, including Chinmo, Rack1, Shi, and Cpb, as regulators of nuclear import of actin [32]. Notably, many of these regulators were conserved in mammalian cells [32], similarly to nuclear actin export regulators reported earlier [33], emphasizing the importance of nuclear actin control.

Taken together, nuclear actin levels are subject to regulation in many physiologically relevant processes. Functionally, reduced nuclear actin levels seem to lead to reduced overall transcription [21,27], whereas increased nuclear actin is used at least for structural support as a filamentous actin network [24], and via unknown mechanisms to regulate specific gene expression programs [29] and stress response [31]. Further mechanistic understanding of nuclear actin functions is required to understand how changes in actin levels elicit these responses. It should also be remembered that levels of nuclear actin will directly influence its polymerization properties, as discussed in the next chapter. The fact that nuclear actin levels are deregulated, for example, in many cancers [26,28], makes this an exciting avenue for further studies.

Regulation of nuclear actin polymerization for specific transcription programs and maintenance of genomic integrity

It was long believed that F-actin only exists in the cytoplasm, mainly because the visualization of filaments in the nucleus was difficult (reviewed by Plessner et al. [34]). At present, it is well established that actin polymerizes in the nucleus, and that the polymerization is tightly regulated by different ABPs (Figure 2). For example, upon serum stimulation, formins mDia1/2 induce rapid and transient nuclear actin polymerization, which is required for nuclear accumulation of MRTF-A and SRF transcriptional activity [10]. Same formins are also required for nuclear actin polymerization and MRTF-A/SRF activation upon cell spreading [11]. Here, filament formation is also dependent on functional integrin signaling and components of the linker of nucleoskeleton and cytoskeleton complex (LINC), suggesting that cellular adhesion and mechanosensing contribute to nuclear actin dynamics. Another mechanism to influence nuclear actin dynamics and MRTF-A/SRF activity is via regulation of filament depolymerization. MICAL-2, an atypical actin-regulatory protein with monooxygenase activity, catalyzes the disassembly of nuclear F-actin through a redox modification of a conserved methionine residue in actin [35]. MRTF-A/SRF pathway is hence exquisitely sensitive to nuclear actin dynamics but also other transcriptional programs seem responsive. T-cell antigen receptor engagement leads

Figure 2



Regulation of actin polymerization inside the nucleus. (1) Nucleus has three different actin pools; monomeric and polymeric actin pools and a pool of actin monomers in stable complexes, such as chromatin remodeling complexes. (2) Actin can also form F-actin puncta, yet it is not known how these short filaments assemble from monomeric actin, and also their relationship with other filaments remains unclear. Actin filament polymerization and turnover is tightly controlled by different mechanisms. (3) Serum stimulation and cell adhesion activate filament assembly through the formins mDia1/2. (4) This reduces the levels of G-actin that leads to SRF activation by relieving MRTF-A from the inhibitory actin monomer. (5) The Arp2/3 complex is an actin nucleator that binds to the side of existing filaments to promote new filament growth as a branch, and it has been shown to promote nuclear actin polymerization upon DNA damage repair. The nucleation activity of Arp2/3 is activated by WASP. (6) In addition, FMN2 with spire1/2 function in DNA damage response and polymerize nuclear actin. (7) Actin polymerization by the formin mDia2 is involved in loading CENP-A to centromeres. (8) Mical2 can promote depolymerization of actin filaments through oxidation and cofilin disassembles nuclear actin filaments upon early G1 cell cycle phase. SRF, serum response factor; MRTF-A, myocardin-related transcription factor A.

to nuclear actin polymerization via a pathway that depends on nuclear Ca^{2+} signaling, Arp2/3 complex, as well as its upstream regulators N-Wasp and NIK. Here, nuclear actin polymerization is required for the induction of specific cytokine genes and T-cell effector responses [36], but the mechanisms have not been established. In the future, it will be important to identify nuclear actin responsive transcription factors beyond the MRTF-A/SRF complex, and to elucidate how the functional role of actin in general transcription [4] influences these gene-specific effects.

Dynamic actin filaments in early G1 phase of the cell cycle have been reported by several studies [13,37,38]. Grosse lab showed that these filaments were needed for nuclear volume and chromatin expansion after mitotic exit, and cofilin was shown to control filament disassembly before the cell entered the next step in the cell cycle [37]. Fisher lab suggested that actin dynamics and formin activity would be required for DNA replication by controlling nucleocytoplasmic transport, loading of replication factors onto chromatin, as well as by controlling both replication initiation and elongation [13]. Another function for the nuclear actin filaments in G1 has been suggested by the Mao lab. They had earlier demonstrated that the formin mDia2 is required for loading of centromere-specific histone H3 variant, CENP-A, to chromatin, which is an important mechanism to define the centromeres epigenetically [39]. The nuclear actin filaments nucleated by mDia2 contribute to the process by constraining centromere movement, thereby facilitating the loading process [38]. Precise control of nuclear actin polymerization during cell cycle seems therefore essential for many different processes. Further studies are required to clarify the signaling pathways regulating nuclear actin and to understand in

molecular detail, how the nuclear actin filaments operate in these contexts.

Nuclear actin polymerization upon DNA damage response has recently gained a lot of attention. First, Mullins-lab demonstrated formin-2 and Spire1/2-dependent formation of nuclear actin filaments and suggested they might be involved with nuclear oxidation upon DNA damage [14]. Another study demonstrated that phosphoinositides, which regulate many ABPs in the cytoplasm, accumulate at DNA damage sites, and recruit formins (mDia2) to assemble nuclear actin filaments [15]. This then mediates the recruitment of the DNA repair protein ATR to the damage sites. Two labs recently discovered that actin-nucleating Arp2/3 complex is involved in nuclear actin polymerization and contribute to the movement of specific double strand breaks (DSBs) during DNA damage response. The Gautier lab showed that nuclear F-actin, WASP, and the Arp2/3 complex are recruited to damaged chromatin undergoing homology-directed repair, and that the actin polymerization is needed for clustering of DSBs into repair sites [17]. The Chiolo lab reported that the relocalization of DSBs in heterochromatin requires also nuclear myosins associated with the heterochromatin repair complex Smc5/6 and the myosin activator Unc45 in *Drosophila* cells. Defects in this pathway cause impaired heterochromatin repair and chromosome rearrangements [16]. Curiously, LINC complex has also been implicated in DSB clustering [40], and a recent study demonstrated that LINC complex is required, together with the actin pathway, for the mobilization of DSBs in ribosomal DNA, perhaps via nuclear envelope invaginations that often contact the nucleolus [41]. Collectively, these studies indicate that nuclear actin polymerization is required for the mobilization of DSBs that are difficult to repair to safe nuclear compartments.

Nuclear actin has also been implicated in other chromatin movement events. Earlier studies had suggested a role for actin in the repositioning of an inducible chromatin loci from the nuclear periphery to the nuclear interior upon transcriptional activation [42], movement of HSP70 transgene toward nuclear speckles [43], and U2 gene locus toward Cajal bodies [44]. A recent study in yeast on the movement of the *INO1* locus may provide a mechanistic basis for these processes [18]. Activation of the *INO1* promoter results in the movement of the locus toward nuclear periphery with a speed of 100 nm/s, which resembles that of motor-dependent cargo transport in the cytoplasm. In support of this, the yeast nuclei contains a dynamic pool of short actin filaments, which are regulated by ABPs such as formin Bnr1, WASP inhibitor Lsb1, and tropomyosin Tpm1. The *INO1* movement depends on both transcription factor-bound nuclear myosin activity and association between Arp-containing chromatin remodeling complexes with actin filaments. These interactions are regulated by chaperones, such as HSP90 [18]. Further studies are required to validate this mechanism in other experimental system, and to clarify the molecular details, such as how the chromatin remodeling complexes interact with actin filaments.

Conclusion

Our knowledge on nuclear actin has grown a lot during the past few years. At present, it is clear that nuclear actin participates in essential nuclear processes, such as gene expression and DNA damage response, although mechanisms still need to be solved. For a long time, nuclear actin pool was thought to consist exclusively of monomers. However, recent studies have established a functional role for nuclear actin filaments and demonstrated that these filaments are dynamic and specific to certain contexts. In the cytoplasm, hundreds of ABPs regulate different aspects of actin dynamics, but only few of them have been shown to control nuclear actin also. In the future, it is therefore important to decipher the full repertoire of proteins that control nuclear actin polymerization. Equally important is to understand the molecular mechanisms by which the nuclear actin filaments operate. Actin constantly shuttles in and out of the nucleus, and the balance between cytoplasmic and nuclear actin pools is tightly regulated, as well as dynamically connected. Levels of nuclear actin have been shown to change in certain conditions, such as in quiescence and differentiation, but the upstream regulatory pathways controlling nuclear actin levels are unclear. Further studies are also required to elucidate, how fluctuating nuclear actin levels influence all nuclear processes that depend on nuclear actin, and what are the mechanisms thereof. In addition, post-translational modifications of nuclear actin and ABPs are currently poorly understood. New discoveries of the post-translational modification status of nuclear actin might give us more knowledge of actin functions and regulation in the nucleus.

Credit author statement

Alise Hyrskyluoto: Writing - Original Draft, Writing - Review & Editing, Visualization, Funding acquisition

Maria Vartiainen: Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition

Conflict of interest statement

Nothing declared.

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** of outstanding interest

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